Remarks

Claims 1-89 are pending. Claims 76-89 are under examination. Claims 1-9 and 64-69 have been canceled. Claims 10-63 and 70-75, drawn to non-elected inventions, have been withdrawn from consideration. Claims 76, 82, 88, and 89 have been amended herein. Support for amending the claim 76, 88, and 89 language "peptide" in the preamble to "peptide with a high affinity for glycosaminoglycans and proteoglycans" is found at page 5, lines 1-11, page 18, lines 21-22, Figs., 1, 2, and 5-7, the Examples and in claims 1, 9, 68, and 69 of the application as filed. Support for amending the claim 82 and 89 language "except that a single cysteine residue is contained in said synthetic peptide at a position within three amino acid residues of the N-terminus or the C-terminus of said synthetic peptide" to "~~except~~ provided that a single cysteine residue is contained in said synthetic peptide at [[a]] an X position within three amino acid residues of the N-terminus or the C-terminus of said synthetic peptide" is found at page 5, lines 12-19, page 24, lines 11-18, Tables I-III, and claims 3, 9 and 69 of the application as filed.

Response to Incorporation of New Matter Rejection

Claims 76-89 stand rejected as allegedly incorporating new matter. The Examiner agrees that the specification and claims as filed provide adequate written description for peptides of the disclosed motifs having high affinity for glycosaminoglycans and proteoglycans. However, the Examiner alleges that the amended claims (amended in the Response mailed December 18, 2003) recite only peptides comprising the disclosed motifs. The Examiner asserts that the amended claims encompass a larger genus of peptides which do not exhibit proteoglycan or glycosaminoglycan affinity.

Independent claims 76, 88, and 89 have been amended herein to recite "peptide with a high affinity for glycosaminoglycans and proteoglycans", which is the language recited in the claims as filed. Support for this amendment is found at page 5, lines 1-11, page 18, lines 21-22, Figs., 1, 2, and 5-7, the Examples and in claims 1, 9, 68, and 69 of the application as filed.

Applicants submit that claims 76-89 as amended herein are definite and that one of ordinary skill in the art would understand that the recited peptides have a high affinity for

glycosaminoglycans and proteoglycans. Applicants request that the new matter rejection be withdrawn.

Response to 35 U.S.C. § 112, second paragraph rejection

Claims 82 and 89 stand rejected as allegedly indefinite. The Examiner asserts that claims 82 and 89 are indefinite for recitation of "a single cysteine residue is contained in said synthetic peptide at a position within three amino acid residues of the N-terminus or the C-terminus of said synthetic peptide". Examiner alleges that it is unclear if the single cysteine residue is an "X" of the recited segments, or if the cysteine residue is in addition to the recited segments.

To clarify the position of the single cysteine residue, claims 82 and 89 have been amended to "~~except~~ provided that a single cysteine residue is contained in said synthetic peptide at [[a]] an X position within three amino acid residues of the N-terminus or the C-terminus of said synthetic peptide". Support for this amendment is found at page 24, lines 11-18, Tables I-III, and claims 3, 9 and 69 of the application as filed. For example, the peptides "ARKKAARA-ARKKACRA" and "ARRAKA-ARRAKA-ARRCKA" disclosed at page 24, lines 1-18, illustrate motifs wherein a single cysteine residue is in an X position within three amino acid residues of the C-terminus.

Applicants submit that claims 82 and 89 as amended are definite and that one of ordinary skill in the art would understand that the single cysteine residue is at an "X" position of the recited segments.

Response to 35 U.S.C. § 103(a) obviousness rejection

Claim 88 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over De Boer et al. (J. Biol. Chem., 1992, 267:2264-2268), in view of Cardin et al. (Arteriosclerosis, 1989, 9:21-13). The Examiner again alleges that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to substitute "A" for "G" in any "X" position in the Lys348-Arg361 peptide of De Boer et al., in view of certain teachings of Cardin et al. Applicants respectfully submit that the combination of De Boer and Cardin does not render amended claim 88 *prima facie* obvious under 35 U.S.C. § 103(a), for the following reasons.

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a prima facie case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). None of these criteria have been met here.

Claim 88, as amended, is drawn to a synthetic concatameric peptide with a high affinity for glycosaminoglycans and proteoglycans, wherein the sequence of amino acid residues is represented by at least two different segments selected from the group consisting of XBBBXXBX, XBXXBBBX, XBBXBX, and XBXBBX; each segment is separated from an adjacent segment by at least one of any amino acid residue;[1] each B is independently selected from the group consisting of arginine and lysine residues; and each X is independently selected from the group consisting of alanine and glycine residues.

The asserted combination of references would not have suggested to one of ordinary skill in the art that they should make the claimed invention. It would not have been *prima facie* obvious to substitute "A" or "G" for any of the positions designated as X in the Lys348 to Arg361 peptide as taught by De Boer. As more fully discussed below, neither De Boer nor Cardin addresses the role or importance of any X position residues, much less the desirability of substituting in alanine or glycine residues at these positions.

[1] The rejection incorrectly states that the segments are separated by at least two amino acids.

Examiner alleges that De Boer teaches that peptide 2 of De Boer, which comprises heparin-binding sequences of vitronectin, contains "both Cardin sites" (Fig. 5).[2] The so-called "Cardin sites" are the 8-mer motif XBBBXXBX and the 6-mer motif XBBXBX. The Examiner's allegation that peptide 2 of De Boer contains both Cardin sites is incorrect. De Boer peptide 2 contains only the 6-mer motif XBBXBX. The second alleged Cardin site of De Boer peptide 2 is not the 6-mer or 8-mer motif of Cardin. Rather, the second alleged Cardin site is a 7-mer, which De Boer mistakenly describes as an XBBBXXB motif. The 7-mer of De Boer is actually the motif BXBBXXB, not "XBBBXXB" as described by De Boer. Regardless, neither 7-mer motif is a Cardin sequence. Therefore, De Boer teaches a peptide with one Cardin site, not a peptide comprising two Cardin motifs, as alleged by Examiner.

Accordingly, although De Boer peptide 2 has two different putative binding segment motifs, e.g., a 6-mer and a 7-mer, De Boer does not teach a peptide comprising a multimer of at least two different segment motifs, wherein the segment motifs are a Cardin 6-mer or 8-mer, or the reverse sequences of the Cardin 6-mer and 8-mer.

De Boer teaches away from the present invention. The ability of a peptide of the invention to bind with heparin is correlated with the ability of the peptide to conform to an α-helix once it binds with heparin (Figs. 3 and 4). The inclusion of alanine in the X position as an α-helix stabilizer was based on the result described in the application that once the peptide bound to heparin, α-helical conformation of the peptide occurred (Figs. 2-4, page 24, lines 3-6, page 38, lines 11-13). Although claim 88 does not recite that alanine in an X position acts as an α-helix stabilizer, it does recite that X is alanine or glycine, and provides examples of peptide motifs comprising alanine in the X position, such as AKKARA and ARKKAAKA (Table 1). The peptides of the present invention only adopt an α-helical conformation upon interacting with heparin and have virtually no intrinsic α-helix structure until binding occurs (see page 32, line 4 to page 33, line 7; Figs. 3 and 4).

The concept of alanine acting as an α-helix stabilizer was not recognized by De Boer or Cardin. In fact, as described above, De Boer does not teach a role for alanine. De Boer

[2] The rejection incorrectly states that peptide 2 has at least one amino acid between each Cardin site. There are in fact two amino acids.

teaches a structurally different peptide than the peptides of the invention. For example, residues 347-353 of vitronectin, part of peptide 2 of De Boer, are in an α-helical conformation, even when not bound to heparin (Hileman et al., BioEssays, 1998, 20:156-167, provided in the Information Disclosure Statement as reference AG). Thus, De Boer teaches away from the present invention's use of alanine, because his teachings would suggest that a peptide of the present invention would not bind to heparin unless the peptide assumed an α-helical conformation in advance of binding to ligand.

Moreover, because the protein binding regions in heparin are randomly distributed, and in some cases sparsely distributed throughout the heparin chain, it would have been counterintuitive to expect that a concatameric peptide of Cardin sequences or reverse Cardin sequences would be effective in binding heparin.

Examiner alleges that De Boer teaches that peptide inhibition of the vitronectin-thrombin-antithrombin complex to endothelial cells is correlated with the ability of said peptide to bind to heparin. Although the Lys345 to Arg361 peptide used by De Boer is derived from the heparin-binding domain of vitronectin, even if one were to conclude that the peptide binds to heparin, De Boer does not teach a direct correlation between the ability of a peptide to bind with heparin and the peptide's ability to inhibit the vitronectin-thrombin-antithrombin complex from binding with endothelial cells.

De Boer Fig. 5 merely demonstrates that certain fragments of vitronectin can inhibit binding of vitronectin-thrombin-antithrombin complexes to endothelial cells. Fig. 5 does not demonstrate that the De Boer synthetic vitronectin fragments bind to heparin or other glycosaminoglycans or proteoglycans. De Boer presents no data regarding peptide binding to heparin. The De Boer statement referred to by the Examiner regarding heparin-binding (page 2267, second column, bridging sentence to page 2268) merely cites Tomassini et al., (Blood, 1986, 68:737-742; copy provided previously) and suggests that there may be a correlation between peptide binding to heparin and peptide binding to a cell. De Boer merely discusses the "potential" of the vitronectin fragments to bind with heparin. In fact, De Boer misstates the relationship between his peptide-cell binding data and the data of Tomassini.

Tomassini merely shows differences in the ability of serum-derived or plasma-derived vitronectin to bind to heparin-agarose in the presence of other proteins. Tomassini does not provide data on the affinity of vitronectin or any other proteins or peptides for non-derivatized heparin, nor does Tomassini discuss a correlation between a peptide binding to heparin and the peptide binding to cells. In addition, Tomassini suggests that vitronectin only binds to heparin-agarose when vitronectin is complexed with thrombin and anti-thrombin III (Tomassini, page 740, column 2).

One of ordinary skill in the art would not view as equivalent: (i) peptide- or protein-complex binding *to a cell*, as taught by De Boer, and (ii) binding of a protein-complex *to a solid-supported heparin* such as heparin-agarose, as taught by Tomassini. The in vitro cellular assay of De Boer is a general assay for detecting the ability of a protein-complex to bind with glycosaminoglycans or proteoglycans. As performed by De Boer, vitronectin-thrombin-anti-thrombin III-complexes bind not just to heparin, but to many different glycosaminoglycans and proteoglycans present on the cell surface or which have been deposited as part of the extracellular matrix. One of ordinary skill in the art would understand that the binding affinity of the protein-complex for the various glycosaminoglycans and proteoglycans varies greatly, and that the De Boer data represent an average binding affinity of the protein-complex for all glycosaminoglycans and proteoglycans which are present. The De Boer assay therefore, does not measure the affinity of the protein-complex for heparin. The De Boer assay is a general assay for protein-complex binding to glycosaminoglycans and proteoglycans.

The solid-support heparin adsorption chromatographic assay used by Tomassini is not a general assay for glycosaminoglycans and proteoglycans. In the Tomassini assay, the protein-complex is contacted with heparin conjugated to an agarose support matrix, in the absence of glycosaminoglycans and proteoglycans. The Tomassini assay was used to identify vitronectin and S-protein in serum and plasma samples. In conclusion, one of ordinary skill in the art would not view the peptide- or protein-complex binding *to a cell* as in De Boer as equivalent to a peptide binding *to a non-derivatized heparin* as in Tomassini, particularly where binding to non-derivatized heparin is performed in the absence of other glycosaminoglycans and proteoglycans.

Fig. 5 of De Boer demonstrates that the peptide 2 6-mer, which has 3 X positions, has one alanine residue and no glycine residues. The peptide 2 7-mer has one glycine residue and no alanine residues. Thus, the Examiner correctly observes that De Boer does not teach the instant peptide where X is selected from alanine and glycine. Furthermore, De Boer does not discuss the significance of specific amino acids at *any* position, and merely mentions that X represents the probability of a non-basic residue (p. 2267, 2nd column). In addition, De Boer does not teach that B position residues are lysine or arginine, nor does it teach peptides with high affinity for glycosaminoglycans or proteoglycans.

Examiner alleges Cardin teaches "B" residues represent a relative probability of basic amino acids and that "X" residues represent a relative probability of non-basic amino acids in heparin-binding proteins. Applicant points out that Cardin teaches that "X" is a hydropathic residue, not a non-basic amino acid.

Cardin does not remedy the deficiencies of De Boer. Cardin does not teach or suggest the use of alanine or glycine at any position and only discusses amino acid residues in general terms with respect to their position on the helical face of the peptide and their effect on charge of the peptide (for example, see page 26, left column, lines 1-20). Although Cardin summarizes the amino acid residues present in various heparin-binding peptides in Tables 3 and 4, Cardin never addresses the role of any specific amino acids in X positions. Cardin merely catalogs amino acids found in X positions.

The Examiner asserts that the inclusion of various X residues in a heparin-binding sequence motif can be "deduced" by their absence from the legend of Table 4 of Cardin. The failure of Cardin to calculate the percentage of amino acids in X positions which are not acidic, basic, or aromatic residues, would not suggest to one of skill in the art that these other amino acids should be used in a peptide. For example, alanine and glycine, neither of which are acidic, basic or aromatic residues, are not the predominant X residues in any of the peptides compiled in Tables 3 and 4 of Cardin. Cardin does not suggest that alanine or glycine should be substituted in an X position.

Cardin in fact teaches away from X position alanine and glycine residues. For example, 12 of the 28 XBBBXXBX motif heparin-binding peptides summarized in Table 4 of Cardin do not contain a single alanine or glycine residue (see Table 2 of Cardin). Additionally, alanine and glycine account for only 7.1% and 11.6%, respectively, of the X

position amino acids of the peptides of Cardin Table 4. Cardin similarly demonstrated low percentages of alanine and glycine in heparin-binding peptides comprising the XBBXBX motif (Table 1). For example, 10 of the 19 heparin-binding peptides comprising the XBBXBX motif analyzed by Cardin do not have a single alanine or glycine residue (Table 1). Therefore, the teachings of Cardin suggest that alanine and glycine are not essential to heparin binding and would not motivate one to substitute alanine or glycine in the X positions of the De Boer peptide.

Because neither De Boer or Cardin discuss the significance of alanine or glycine at X positions, and because neither reference teaches a role for X position amino acids in the binding of peptides to heparin or other glycosaminoglycans, it would not have been obvious to deduce various X position residues based on Table 4 of Cardin, nor would it have been obvious to substitute "A" or "G" for any of the positions designated as X in the Lys348 to Arg361 peptide of De Boer.

Cardin teaches that B position residues can be many different amino acids, including non-basic amino acids (Tables 3 and 4). For example, Cardin discloses that one of the B positions of the 6-mer (B-2) and two of the B positions of the 8-mer (B-3 and B-1) comprise amino acid residues other than the basic amino acids arginine and lysine. Therefore, as to the amino acid residues in the B positions, Cardin teaches away from the present invention. According to the present invention, B is selected from arginine and lysine residues.

Even if De Boer and Cardin were combined, the result is not the claimed invention. Neither reference, teaches a synthetic concatameric peptide wherein the peptide comprises at least two different segments selected from the group consisting of XBBBXXBX, XBXXBBBX, XBBXBX, or XBXBBX, and further wherein the peptide does not comprise only XBBBXXBX segments, or only XBXXBBBX segments, or only XBBXBX segments, or only XBXBBX segments. Furthermore, because neither reference teaches or suggests that X position amino acids comprise only alanine or glycine residues or that B positions comprise only arginine or lysine residues, and that such peptides have high affinity for glycosaminoglycans and proteoglycans, combining the references would not result in the claimed invention.

For the reasons described above, the claimed invention would not have been obvious from the combination of De Boer and Cardin. Applicants request the rejection as to claim 88 be withdrawn.

Conclusion

Based on the foregoing, all claims are believed to be in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,
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